<u>REQUEST FOR PROPOSALS (RFP- 09)</u>
Mickey Leland National Urban Air Toxics Research Center

Critical Review of Health Impacts of Metals in Ambient Air Fine Particulate Matter

Release Date: <u>February 19, 2009</u>

I. INTRODUCTION

This announcement is a request for proposals. The Mickey Leland National Urban Air Toxics Research Center (NUATRC or "the Center") is requesting proposals from qualified institutions and individuals for a review of the contribution of air-toxic metals in ambient fine particles to the human health effects associated with particulate air pollution. This project is jointly funded by the NUATRC and the Nickel Producers Environmental Research Association (NiPERA).

The Clean Air Act Amendments (CAAA) of 1990 established a control program for sources of 189 "hazardous air pollutants, or air toxics," which may pose a risk to public health. With the passage of these Amendments, Congress also established the NUATRC to develop and direct an environmental health research program that would result in a better understanding of the risks posed to human health by the presence of these toxic chemicals in urban air.

A number of toxic metals such as antimony, arsenic, beryllium, cadmium, chromium, cobalt, lead, manganese, mercury, nickel, and selenium are among the 187 air toxics now listed in the CAAA. Because many of these toxic metals are also thought to be important components of fine ambient PM, research conducted to understand how the metal content of ambient fine PM contributes to the health effects associated with particulate air pollution will help achieve the goals of the Leland Center.

II. STUDY RATIONALE & OBJECTIVE

NUATRC previously commissioned two studies, Christiani et al. (2006) and Claiborn et al. (2008), to better understand the role that metals in ambient air PM may play in respiratory and cardiovascular disease. These studies revealed that major uncertainties still exist in our understanding of the human health effects from exposure to air-toxic metals in ambient PM. NUATRC therefore solicited input via a Request for Information **(**RFI 2008) regarding key research areas for furthering our understanding of the contribution of air-toxic metals in ambient fine particles to the human health effects associated with particulate air pollution. The NUATRC also received information on other data gaps and areas of inconsistency that should be addressed. The feedback received from RFI 2008 has informed this RFP. The overall objective of this project is to develop a critical review of the current literature on the health effects of fine particulate-associated air-toxic metals.

III. BACKGROUND

Over the last decade, a substantial amount of research has focused on the effects of ambient air particulate matter (PM) on respiratory and cardiovascular disease, particularly for sensitive populations. Many epidemiological studies have suggested a small but statistically significant association between excess human mortality and morbidity and exposure to PM in the urban atmosphere (Dockery and Pope 1994; US EPA 2004).

Fine particles enriched with toxic metals are emitted from a number of sources that include the burning of coal, oil, diesel fuel, gasoline, and wood; transportation; manufacturing; power generation; and space heating. High-temperature industrial processes such as smelting, steel production, and municipal waste incinerators are also significant sources of fine particles that are enriched with toxic metals (Schroeder et al. 1987).

The concentration and relative proportions of these metals in various particle-size ranges depend on a number of factors such as the nature of emissions, the photochemical activity, and meteorology (Finlayson-Pitts et al. 1986). In addition, the chemical form of the metals is important since metals are usually more bioavailable in certain forms than in others**.** In general, studies that chemically characterized fine ambient particles for their metal content have revealed very low concentrations of metals (Clayton et al. 1993; Pritchard et al. 1996; Spengler and Thurston 1983) compared to studies of occupational exposures or laboratory animal studies (Chang 1996; US EPA 2004). Data from occupational studies in humans and laboratory studies in animals suggest that acute exposures to high levels or chronic exposures to low levels (albeit, much higher than those found in ambient fine particles) of particle-bound metals can have adverse effects on the respiratory, immune, or cardiac systems (Chang 1996). For the most part, neither workplace nor animal studies with pure metal substances predict significant adverse effects at the low levels in which metals are found in PM.

Several components such as transition metals, organic constituents, endotoxins, and acid sulfates have been postulated as participating in the biologic response (Ghio and Cohen 2005) associated with particulate air pollutants. Some studies suggest that acute respiratory effects caused by particulate air pollutants may be attributed partly to metal elements causing damage by the generation of free radicals (Prahalad et al. 2000; Roemer et al. 2000). Subsequent events may include epithelial damage, increased permeability, and an inflammatory response leading to lung function decrements (Bergamaschi et al. 2001). However, the contribution of particulates' metal components to acute health effects has not been adequately evaluated (Roemer et al. 2000).

A number of intratracheal instillation studies using residual fly ash or urban particulate matter have demonstrated an association between metal content and the ability to elicit pulmonary inflammation and airway hyperactivity in rats (Dreher et al. 1997; Kodavanti et al. 1997; Spengler and Thurston 1983). Inhaled fly ash induced pulmonary inflammation, chemokine expression in lungs and heart, and caused death in rats with monocrotaline-induced preexisting cardiorespiratory disease that mimicked the human disease (Killingsworth et al. 1997). Residual fly ash from fuel oil was reported to induce cytokines in cultured human airway epithelial cells and the reaction was dependent on the metal content of the fly ash (Carter et al. 1997). Overall, these studies suggest a direct or indirect role of metals in the acute pulmonary or cardiopulmonary injury induced by PM. However, more work is needed in order to relate these findings to the acute mortality and morbidity associated with exposure to fine particles in humans.

A recent study by Hong et al. (2007) demonstrated that metals in particulate pollutants affects peak expiratory flow in schoolchildren Previously, two European studies reported that airborne iron may be associated with a decline in peak expiratory flow rate, production of phlegm, or exacerbation of respiratory symptoms (Dusseldorp et al. 2007; Roemer et al. 2000). While these studies provide some insight into the potential role of toxic metals in contributing to the respiratory, immunologic, or cardiopulmonary effects of ambient particulate air pollution on human health, more information is still needed.

The NUATRC-funded study by Christiani et al. (2006) found that fine particulate exposure and, specifically, soluble transition metals may be partially responsible for the adverse pulmonary responses seen in boiler-makers exposed to residual oil fly ash (ROFA). Their analyses of cardiovascular outcomes suggest that there may be both a long-acting (several hours) and a short-acting (several minutes) component to the mechanism of action following exposure to metal-containing $PM_{2.5}$. The clinical significance of these effects in a healthy working population is, at present, unclear. Their findings regarding specific metals revealed some inconsistencies and were dependent on the averaging time used in the analysis.

The second NUATRC-funded study, by Claiborn et al. (2008), found limited evidence for health effects from combustion-related air pollution (including carbon monoxide (CO), total $PM_{2.5}$, and total carbon (TC)), and no association between total respiratory emergency department (ED) visits and any of the metals of interest. These included those associated with specific combustion sources such as Zn (a tracer/marker for a motor vehicle source) and As (a tracer/marker for a wood smoke source). In addition, other metal species found in Spokane fine PM, along with TC, were investigated and showed an overall lack of association with all respiratory ED visits, except Zn, for which an increased relative risk was found at the 2- and 3-day lags. TC was found to be significantly associated with all respiratory ED visits at 1-, 2-, and 3-day lags.

Finally, during the course of seeking input on NUATRC RFI 2008, three review papers analyzing the associations between adverse health effects of fine PM constituents were published. Schlesinger (2007) reviewed the health effects associated with inorganic constituents; Mauderly and Chow (2008) looked at organic aerosols. Chen and Lippmann (2009) reviewed the literature on health effects caused by inhalation of metal-associated PM. Their review indicates that ROFA is the most toxic source-related mixture; nickel and vanadium (characteristic tracers of ROFA) appear to be particularly influential components in terms of acute cardiac function changes and excess short-term mortality (Chen and Lippmann 2009). They also highlight evidence that other metals within ambient air PM, such as lead and zinc, may also affect human health though they caution that most evidence available now is based on the use of ambient air data – not actual exposures – so it is difficult to determine associations and/or effect coefficients. They caution that there are considerable uncertainties about causality, due to exposure misclassification and measurement errors. The paper does not address the extent of confounding of the ROFA effect with Ni, V, and organics, and there is no mention of the size of the effect of the metals. Furthermore, there is little or no information on ambient versus actual exposure to PM-associated metals, details on the variation from city to city, or information distinguishing between effects from $PM_{2.5}$ and PM_{10}.

It may be of interest to note that two NUATRC-funded studies (Kinney et al. 2005, 2008; Turpin et al. 2007) have characterized indoor, outdoor, and personal exposures of the soluble fraction of selected metals in fine particulate matter. Databases for these studies (available at: http://teach.aer.com/ and http://riopa.aer.com/, respectively) may shed some light on how ambient air exposures differ from actual human exposure to fine PM-associated toxic metals.

IV. Scope of Work:

Building upon the work of Chen and Lippmann (2009), and the NUATRC-funded studies by Christiani et al (2006) and Claiborn et al. (2008), NUATRC seeks a critical review that moves beyond hazard identification to exposure assessment and dose-response so that results can be integrated into a future risk analysis. Potential applicants should use these publications as their starting point for identifying potentially useful and relevant studies for their analyses.

The following metals associated with PM appear most frequently in the literature and are therefore more amenable to review: As, Cr, Cu, Fe, Mn, Ni, Pb, Se, Ti, V and Zn. Since lead was completely phased out of gasoline by 1996 and current ambient sources are local point sources such as smelters and battery plants, we suggest omitting it from the list. We recognize that the literature on the metals of interest could be voluminous, but the studies containing exposure and dose-response data are few and can be used as guiding point to further identify most relevant studies**.** It is important to establish a strategy for selecting the particular metals of primary concern or organize the review so that appropriate funding, time and effort may be dedicated accordingly. Examples of some such strategies could be:

- The metals might be grouped based on (1) commonalities in mode of action and within specific endpoints, (2) common combustion sources such as those coming from internal combustion engines such as gasoline and diesel; wood and coal combustion for power; and industrial processes such as smelters and waste incineration.
- For evaluation of toxicological and human studies, it may be appropriate to focus on certain metal constituents because they are predominantly found in most ambient $PM_{2.5}$, rather than focusing efforts on metals that are rarely found in the ambient $PM_{2.5}$ fraction.

Specific areas for consideration include, but are not limited to, the following:

Which metals are most commonly found in ambient particulate matter (PM) in the size of interest?
We recommend limiting the review to studies that evaluated $PM_{2.5}$ due to insufficient evidence linking health problems to long-term exposure to coarse particles. However there are some studies evaluating the contribution of Ni and V in PM_{10} to risk of morbidity and mortality **(**Dominici et al, 2007). Information distinguishing between metals associated with $PM_{2.5}$ versus PM_{10} would be useful. Further, there is mounting toxicological evidence that, once inhaled, ultrafine particles may act quite differently from fine particles (Elder and Oberdorster, 2006). We recognize that while the review will focus on $PM_{2.5}$, it may also be important to consider studies on PM_{10} and ultrafine particles. The scope of the present study does not include consideration of nanomaterials.

What is known about the chemical speciation of metals in PM?
When considering plausible biological mechanisms of injury, PM mass or other physical or chemical properties of PM have been considered as the causal factors associated with the observed health outcomes. Studies have found associations with PM chemical constituents such as trace elements and metals such as silicon (Wellenius et al. 2003), vanadium (Saldiva et al. 2002), iron, nickel, and zinc (Burnett et al. 2002). Chemical characteristics such as oxidation state, solubility, and acidity solubility may be central to toxic effects. Understanding the characteristics of the complex chemical mixture in the fine fraction is important as the combination of several physical or chemical properties of PM may be associated with the observed health effects.

What is known about the sources of the various metals present in PM?
In recent years, air pollution studies have focused on human health effects associated with sources of urban air pollution such as traffic and industrial sources, such as smelting or coal combustion from electrical utilities. Epidemiological studies involving source apportionment techniques have been used to investigate and generate hypotheses about daily mortality associated with sources of $PM_{2.5}$ air pollution.

What have human studies demonstrated regarding the role of metals in PM in human disease?
Few studies have been conducted to specifically correlate individual metal constituents of PM with adverse health effects, and the scientific evidence on the human health impact of PM constituents is limited. The literature review will therefore be limited to those studies that have been conducted to specifically have information on dose-response of metal constituent(s) with adverse health effects. It will not be designed to evaluate the health effects of the listed metal constituent per se. It is also important to distinguish between those studies that clearly implicate a metal as a toxic agent in contrast to those that implicate a source/mixture that includes the metal being considered. Further, ambient versus actual exposure to PM-associated metals should be considered. It will be important to discuss what is known about how ambient air exposures differ from actual human exposures to PM-associated metals and their implication for human health effects.

What have animal models shown regarding the role of specific metals in PM and PM-associated health effects, and at what levels?
This information will contribute to the understanding of what specific constituents may be responsible for the effects observed in humans exposed to PM. Such information is difficult to discern from epidemiological studies. The literature review will be limited to those toxicological studies that have specifically focused on discerning the dose-response of individual metals, preferably in the same chemical form in which they are expected to be present in PM.

What *in vitro* studies have been used to study the effects of metals associated with PM?
Few studies have focused on the *in vitro* toxicity of metal constituents specifically as components of PM. While not a high priority aim, information on dose-response relationships and comparison of *in vitro* responses to PM to responses to pure metals (in the same chemical form in which they are expected to be present in PM) may also be included.

What is known about the way in which metals in PM interact with the respiratory tract and how they may be absorbed into the systemic circulation?
The relevance of animal and *in vitro* studies to human health in terms of bioavailability, route of exposure, and dose should be discussed.

What do these studies (human, animal studies -- both *in vivo* and *in vitro*) report regarding the commonalities in mode of action among groups of metals, and within specific endpoints?
Does a consistent picture emerge about the specific health effects induced by metals in PM across *in vitro* and *in vivo* toxicological and epidemiologic studies? How does that relate to the general role of metals in human diseases based on a potentially new subset of studies not previously reviewed? Analyzing the already reviewed studies on metals and health effects is beyond the scope of this work. Finally, note how the individual variations in responsiveness to metals in fine PM (i.e., age, illness, genetic makeup) may affect toxicity.

What is a proposed research agenda to address key uncertainties and research gaps?
What are some of the data gaps and areas of inconsistency on the current state of the science related to the health effects of fine PM-associated air toxic metals? What type of research is needed to address these issues?

V. SPECIFIC REQUIREMENTS

ELIGIBILITY:
Investigators who are either faculty members with appointments at academic research institutions or scientists of equivalent rank in research centers and private consulting companies will be considered. Minorities and women are particularly encouraged to apply. Foreign institutions are not eligible to apply.

MECHANISM OF SUPPORT:
A five month contract will be awarded to each individual whose proposal is accepted by the NUATRC, or the institution with which the individual is affiliated. Continued support for this project is subject to availability of funds and progress achieved.

FUNDS AVAILABLE:
The estimated total funds (direct and indirect costs) that may be requested for this project are $50,000. It is anticipated that one project will be funded in response to this RFP. Funding of a proposal will be dependent on the receipt of a sufficient number of meritorious proposals and availability of funds.

REPORT:
The Contractor will provide an Interim Report after 3-months of work. In lieu of a Final Report, at the completion of the project the contractor should prepare a manuscript based on the project for publication in a peer-reviewed journal. The contractor should notify the NUATRC as to the journal(s) under consideration prior to submitting the manuscript. When the manuscript is submitted for publication by the contractor, a copy should be submitted to the NUATRC at the same time. A notice from the journal stating that the manuscript has been accepted for

publication will serve as a substitute for a Final Report and the Center's acceptance of the Final Report.

PROPOSALS:

Prospective applicants must submit a proposal on or before March 20, 2009. The proposal should not exceed 20 pages and should include the following: names and titles of the Principal Investigators and any Co-Investigators, and brief descriptions of the proposed studies. Proposal will be judged by a subgroup of the Center's Scientific Advisory Panel for their responsiveness to the objectives of the RFP, qualifications of the Investigators, previous experience with similar work, and adequacy of time and budget management.

Please submit electronic response to:

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A preliminary timeline for this project is as follows:

Release of RFA: February 19, 2009
Response to RFA: March 20, 2009
Contract and Commence work: May 4, 2009
End work: October 9, 2009

VI. REFERENCES

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